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MEETING ABSTRACT Open Access

Toxicity of ascaridole from *Chenopodium ambrosioides* in mammalian mitochondria

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Background

Chenopodium ambrosioides has been used in traditional American medicine against parasitic diseases. Its essential oil (EO) is still used to treat leishmaniasis although it exhibits toxic effects in mammalian cells. Therefore, we studied the toxic mechanism of EO and its major pure ingredients (carvacrol, caryophyllene oxide and ascaridole) in mammalian cells and mitochondria.

Methods

Ascaridole was synthesized from alpha-terpinene and characterized by NMR and IR spectroscopy. The toxic effects of these compounds on macrophages from BALB/c mice and on the bioenergetics of submitochondrial particles from bovine heart (SMP) and rat liver mitochondria (RLM) were studied. Toxic radical intermediates arising from the endoperoxide ascaridole were characterized by ESR spectroscopy.

Results

The MTT assay, which relies on mitochondrial function, revealed that caryophyllene oxide (IC_{50} = 9.7 ± 4 μM) and ascaridole (IC_{50} = 32 ± 8 μM) inhibited the survival of peritoneal macrophages from BALB/c mice *in vitro* more than the EO. In SMP we observed that all products inhibited mitochondrial respiration stronger for complex I than for complex II substrates. Most active in this respect was caryophyllene oxide, which preferably inhibited the complex I activity (IC_{50} = 92 ± 6 μM). The pure compounds were more inhibitory for oxidative phosphorylation in RLM than EO. In the absence of Fe^{2+}, ascaridole (IC_{50} > 612 μM) was less toxic to RLM than other major ingredients. However, it was shown that Fe^{2+} potentiated the toxicity of EO and ascaridole on oxidative phosphorylation of RLM. Evidence for the formation of carbon-centered radicals in the presence of Fe^{2+} has been obtained by ESR/spin trapping. To explore the route of ascaridole activation different iron-containing proteins were tested by ESR/spin trapping. Neither reduced nor oxidized mitochondrial cytochrome c as well as oxidized hemin were able to cleave ascaridole significantly. However, reduced hemin efficiently produced carbon-centered radicals from ascaridole. Since detoxification of ascaridole by mammalian antioxidative enzymes is rather slow, hemin-mediated ascaridole cleavage contributes to its toxicity.

Conclusions

These data suggest that the toxicity of the essential oil from *Chenopodium ambrosioides* is partially related to the inhibition of the respiratory chain preferably by caryophyllene oxide while the toxicity of the antiparasitic agent ascaridole is dependent on the availability of redox-active iron.

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